Meta-analysis of antibiotics *versus* appendicectomy for non-perforated acute appendicitis

V. Sallinen[1,2], E. A. Akl[4,6], J. J. You[6,7], A. Agarwal[6,8], S. Shoucair[5], P. O. Vandvik[9], T. Agoritsas[6,10], D. Heels-Ansdell[6], G. H. Guyatt[6,7] and K. A. O. Tikkinen[3]

Departments of [1]Abdominal Surgery and [2]Transplantation and Liver Surgery and [3]Urology and Public Health, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [4]Department of Internal Medicine, American University of Beirut, Beirut, and [5]University of Balamand, Tripoli, Lebanon, Departments of [6]Clinical Epidemiology and Biostatistics and [7]Medicine, McMaster University, Hamilton, and [8]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, [9]Department of Medicine, Innlandet Hospital Trust, Gjøvik, Norway, and [10]Division of General Internal Medicine, Department of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland
Correspondence to: Dr K. A. O. Tikkinen, Department of Urology, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 4, 00029 Helsinki, Finland (e-mail: kari.tikkinen@gmail.com)

Background: For more than a century, appendicectomy has been the treatment of choice for appendicitis. Recent trials have challenged this view. This study assessed the benefits and harms of antibiotic therapy compared with appendicectomy in patients with non-perforated appendicitis.

Methods: A comprehensive search was conducted for randomized trials comparing antibiotic therapy with appendicectomy in patients with non-perforated appendicitis. Key outcomes were analysed using random-effects meta-analysis, and the quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results: Five studies including 1116 patients reported major complications in 25 (4·9 per cent) of 510 patients in the antibiotic and 41 (8·4 per cent) of 489 in the appendicectomy group: risk difference −2·6 (95 per cent c.i. −6·3 to 1·1) per cent (low-quality evidence). Minor complications occurred in 11 (2·2 per cent) of 510 and 61 (12·5 per cent) of 489 patients respectively: risk difference −7·2 (−18·1 to 3·8) per cent (very low-quality evidence). Of 550 patients in the antibiotic group, 47 underwent appendicectomy within 1 month: pooled estimate 8·2 (95 per cent c.i. 5·2 to 11·8) per cent (high-quality evidence). Within 1 year, appendicitis recurred in 114 of 510 patients in the antibiotic group: pooled estimate 22·6 (15·6 to 30·4) per cent (high-quality evidence). For every 100 patients with non-perforated appendicitis, initial antibiotic therapy compared with prompt appendicectomy may result in 92 fewer patients receiving surgery within the first month, and 23 more experiencing recurrent appendicitis within the first year.

Conclusion: The choice of medical *versus* surgical management in patients with clearly uncomplicated appendicitis is value- and preference-dependent, suggesting a change in practice towards shared decision-making is necessary.

Introduction

Acute appendicitis is the most common indication for emergency abdominal surgery worldwide: approximately one in every ten individuals will have acute appendicitis during their lifetime[1]. In the UK alone, approximately 40 000 appendicectomies are performed every year. Although appendicectomy is a routine surgical procedure with low mortality, 5–28 per cent of patients develop a complication[2].

Since surgeons identified appendicitis as a source of pelvic sepsis and subsequent high mortality, appendicectomy has been considered mandatory[3,4]. In 1956, Coldrey[5] challenged this view in a report of 137 patients with acute appendicitis for more than 24 h treated with antibiotics rather than surgery. In 1977, researchers from China[6] reported successful treatment of 92·9 per cent of 425 patients with acute appendicitis by traditional Chinese medicine alone. Nevertheless, appendicectomy remained the standard treatment for appendicitis[7].

Another challenge to convention appeared in 1995 when a small randomized clinical trial (RCT)[8] comparing antibiotics with appendicectomy suggested no difference

in efficacy. In the past 10 years, improved CT, allowing more accurate diagnosis of acute appendicitis and preoperative differentiation of perforated *versus* non-perforated appendicitis, has encouraged the conduct of additional RCTs[9−14].

A number of systematic reviews[15−25] have attempted to synthesize the published evidence. However, earlier systematic reviews were limited by varying outcome definitions for antibiotic treatment *versus* surgery[18,22,23], inclusion of retracted studies[22,23,25], and inclusion of a study[11] at very high risk of bias[16,22,25]. Furthermore, since the publication of the most recent meta-analysis[15], the results of two additional eligible RCTs have become available[13,14].

The present systematic review and meta-analysis evaluated the relative merits of antibiotic therapy *versus* appendicectomy in patients with acute non-perforated appendicitis. The approach was to consider the studies in a practical or pragmatic way, rather than using a mechanistic or explanatory perspective[26]. The interest was not in comparing appendicectomy with an antibiotic for all management, but rather in comparing a management strategy of immediate appendicectomy *versus* the clinically sensible alternative of antibiotics initially, with appendicectomy as necessary, depending on the response to antibiotics. This perspective guided presentation of the results.

Methods

Eligibility of studies

RCTs that compared antibiotic treatment with appendicectomy in patients with suspected acute non-perforated appendicitis were included. Quasi-RCTs were also included, but only in the sensitivity analysis. Studies with a very high risk of bias, in which both the description of methods and the baseline characteristics indicated that many patients randomized were not included, were excluded.

Data sources and searches

The comprehensive search conducted in the 2011 Cochrane systematic review of Wilms and colleagues[22], which extended until June 2011, was updated. This consisted of three blocks of search terms for the concepts appendicitis, appendicectomy and antibiotic treatment, limited by the Cochrane filters for RCTs and the McMaster University Health Information Research Unit Clinical Queries hedges for therapeutic studies. The searches were adapted and run without language restrictions in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1 January 2011

to 4 December 2015. PubMed was also searched for in-process citations, and the major clinical trial registries (ClinicalTrials.gov: http://clinicaltrials.gov/; International Clinical Trials Registry Platform Search Portal (ICTRP): http://apps.who.int/trialsearch/) were searched for ongoing trials. *Appendix S1* (supporting information) shows details of the search strategy. In addition, reference lists of other previous systematic reviews[15−21,23,24] comparing antibiotic treatment with appendicectomy in patients with non-perforated appendicitis were searched.

Study selection

Using standard, pilot-tested forms and working in teams of two, reviewers screened all titles and abstracts identified by the literature search independently, and obtained full-text articles of any article identified as potentially eligible by either reviewer. The reviewers used standard, pilot-tested forms to evaluate the full texts for eligibility and resolved disagreement by discussion or, if necessary, by consulting with a third reviewer.

Data extraction

Using standard pilot-tested forms along with detailed instructions and working in teams of two, reviewers extracted data independently. A clinician–methodologist adjudicator resolved disagreements. Finally, authors were contacted to check the data for accuracy, and to provide additional information regarding the original studies, when needed.

The following data were extracted: sample size, participants' characteristics, antibiotic regimens and details of surgical management (laparoscopic or open, any antibiotic use), and the following outcomes (for both treatment groups): major complications at 1 year, including Clavien–Dindo complication classification grade III or above (conditions requiring endoscopic, radiological or surgical intervention, or causing organ dysfunction or death), such as appendiceal perforation, as well as deep infections, incisional hernias and adhesive bowel obstruction not requiring intervention; minor complications at 1 year, such as superficial wound infections, diarrhoea and abdominal discomfort; confirmed or suspected recurrence of appendicitis between 1 month and 1 year; rate of appendicectomy within 1 month of intervention; duration of hospital stay; and duration of sick leave.

Risk of bias

In the risk-of-bias assessment, each study was evaluated using a modified version of the Cochrane Collaboration's
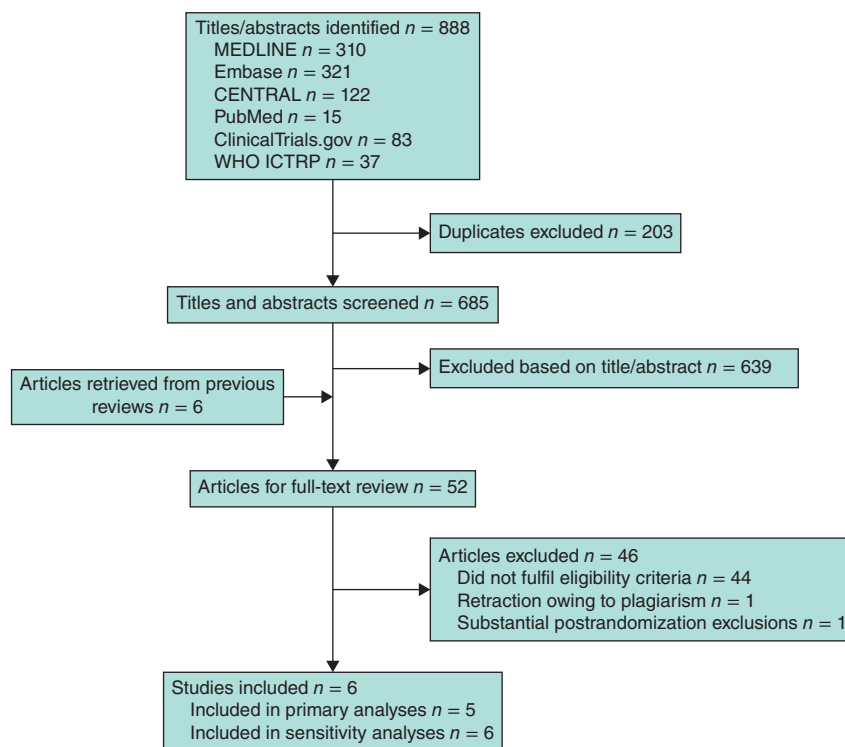
Fig. 1 Flow chart showing selection of articles for review. WHO, World Health Organization; ICTRP, International Clinical Trials Registry Platform Search Portal

instrument[27] according to four criteria: random sequence generation, allocation concealment, blinding and completeness of data. For each criterion, studies were judged to be at either high or low risk of bias.

Statistical analysis

Complete-case analyses were carried out (including only patients who were followed and whose outcomes were available). Pooled estimates of risk differences were calculated by a random-effects meta-analysis using the DerSimonian and Laird approach (Freeman–Tukey double arcsine transformation). Heterogeneity was assessed for each outcome across studies using the I^2 statistic and Cochran's Q. For outcomes in which five or more studies were available, subgroup analyses were planned to examine the study level variables as potential sources of heterogeneity. These variables and the pre-specified hypotheses that results would favour antibiotics were: those with CT confirmation of the diagnosis of non-perforated appendicitis; and those with low risk of bias (separately for each risk-of-bias domain with at least 2 studies with high and at least 2 studies with low risk of bias).

For outcomes in which there was a significant difference between groups, sensitivity analyses were planned in which results were imputed for missing data in a manner that challenged the robustness of these differences[28–30]. If missing data were minimal (5 per cent or less), the plan was not to conduct these analyses.

Quality of evidence assessment

Guidance from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group[31,32] provided the methodology for assessing quality of evidence.

Results

The search yielded 685 potentially relevant reports. After screening titles and abstracts and trial registries, and including six studies[8–12,33] in previous reviews[15–25] (*Fig. 1*), 52 reports were retrieved for full-text screening, of which a total of six RCTs were included: five in the final primary analysis[8,9,12–14] and, in addition, one quasi-RCT[10] in a sensitivity analysis. Two RCTs were excluded: one because of subsequent retraction owing to plagiarism[33] and

Table 1 Characteristics of the included studies

Reference	Study design	Participants	Intervention (antibiotic therapy)	Control (appendicectomy)	Outcomes assessed	Funding and conflict of interest statement
Eriksson and Granström[8]	Single-centre randomized trial	Patients (*n* = 41) aged 18–75 years with history and clinical signs of acute appendicitis, positive findings at ultrasonography, and raised levels of inflammatory markers (CRP or WBC)	Intravenous cefotaxime 2 g twice daily and tinidazole 800 mg once daily for 2 days, followed by oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 8 days. Proceeded to appendicectomy based on clinician's judgement – no prespecified criteria	Open appendicectomy (100%) Antibiotics given only to patients with perforation or abdominal spillage	Appendicectomy rate within index admission. Success of treatment. Complications (at 1 year). Recurrence (at 1 year). Length of stay. Pain (VAS). Pain (use of medication)	Funding: Karolinska Institute, Swedish Hoechst, Pfizer, Mutual Group Life Insurance Company Förenade Liv. No conflict of interest reported
Salminen *et al.*[13]	Multicentre randomized trial	Patients (*n* = 530) aged 18–60 years admitted to the emergency department with clinical suspicion of uncomplicated acute appendicitis diagnosed by CT. Excluded if any of the following: appendicolith, perforation, abscess or suspicion of tumour	Intravenous ertapenem sodium 1 g once daily for 3 days, followed by oral levofloxacin 500 mg once daily and metronidazole 500 mg three times per day for 7 days. Appendicectomy performed if progressive infection, perforated appendicitis or peritonitis suspected on examination within 12–24 h after admission	Open (94%) or laparoscopic (6%) appendicectomy with prophylactic antibiotics. Postoperative antibiotics given only in patients with suspected wound infection	Primary outcome. Antibiotic group: resolution of appendicitis resulting in discharge from hospital without need for surgical intervention and no recurrent appendicitis during a minimum follow-up of 1 year. Appendicectomy group: successful appendicectomy. Secondary outcomes. Overall postinterventional complications. Late recurrence after 1 year (unreported*). Length of stay. Length of sick leave. Postoperative pain (VAS). Use of pain medication (unreported*)	Funding: Government research grant (EVO Foundation) awarded to Turku University Hospital. Dr Salminen reported receiving personal fees for lectures from Merck and Roche; no other disclosures
Styrud *et al.*[9]	Multicentre randomized trial	Men (*n* = 252) aged 18–50 years with clinically suspected acute non-perforated appendicitis and CRP > 10 mg/l	Intravenous cefotaxime 2 g twice daily and tinidazole 800 mg once daily for 2 days, followed by oral ofloxacin 200 mg and tinidazole 500 mg twice daily for 10 days. Proceeded to appendicectomy based on clinician's judgement – no prespecified criteria	Open (94%) or laparoscopic (6%) appendicectomy. Unclear whether prophylactic or postoperative antibiotics given	Appendicectomy rate within index admission. Success of treatment. Complications (at 1 year). Recurrence (at 1 year). Length of stay. Length of sick leave. Pain (unreported*)	Funding: Swedish Society of Medicine, Karolinska Institute, Wallenius Corporation, Aventis Pharma. No conflict of interest reported
Svensson *et al.*[14]	Single-centre randomized (pilot) trial	Children (*n* = 50) aged 5–15 years with clinical diagnosis of acute appendicitis. Exclusion criteria: Suspicion of perforated appendicitis on the basis of generalized peritonitis. An appendiceal mass diagnosed by clinical examination and/or imaging. Previous non-operative treatment of acute appendicitis. All patients had at least one ultrasound examination, 4 had CT	Intravenous meropenem 10 mg/kg three times daily and metronidazole 20 mg/kg once daily for at least 48 h. Once the child was well clinically and tolerating oral intake, antibiotics continued with oral ciprofloxacin 20 mg/kg twice daily and metronidazole 20 mg/kg once daily for 8 days. Proceeded to appendicectomy based on clinician's judgement – no prespecified criteria	Laparoscopic appendicectomy (100 per cent). Prophylactic antibiotics given to all. Intravenous antibiotic continued for 24 h to patients with gangrenous appendicitis and for 3 days in those with perforated appendicitis	Primary outcome: resolution of symptoms without significant complications (defined as length of stay over 7 days, abscess, need for surgery within 48 h (antibiotic group only), recurrence of appendicitis within 3 months, or negative appendicectomy). Secondary outcomes. Length of stay. Other complications (wound infection, wound dehiscence, diarrhoea, etc.). Recurrent appendicitis at 1 year. Total costs	Funding: Crown Princess Lovisa's Foundation, the Hirsch Foundation. No conflict of interest reported

Table 1 continued on next page

Table 1 continued

Reference	Study design	Participants	Intervention (antibiotic therapy)	Control (appendicectomy)	Outcomes assessed	Funding and conflict of interest statement
Vons et al.[12]	Multicentre randomized trial	Patients (*n* = 243) aged 18–68 years with uncomplicated acute appendicitis, diagnosed by CT	Amoxicillin plus clavulanic acid 3–4 g per day for 8–15 days, intravenously to those with nausea or vomiting, and orally to all others. Appendicectomy undertaken if: Symptoms and abdominal tenderness failed to resolve after 48 h. Persistence of pain or fever at 8 days prompted CT and possible appendicectomy *or* Sustained high WBC or high CRP concentration on day 15 prompted appendicectomy without additional CT	Open (34%) or laparoscopic (66%) appendicectomy with single-dose prophylactic antibiotics. Postoperative antibiotics given if complicated appendicitis found	Primary outcome: occurrence of peritonitis within 30 days of initial treatment (defined as perforated appendicitis in antibiotic group, postoperative peritonitis in appendicectomy group). Secondary outcomes. Complications (other than peritonitis) at 1 year. Recurrence (defined as appendicectomy performed between 30 days and 1 year, with confirmed diagnosis of appendicitis). Pain (number of days with VAS 4 or more). Length of stay. Length of sick leave	Funding: French Ministry of Health, Programme Hospitalier de Recherche Clinique 2002. No conflict of interest reported

CRP, C-reactive protein; WBC, white blood cell count; VAS, visual analogue scale. *Outcome prespecified as a secondary outcome but no data presented in publication.

Table 2 Risk of bias

Reference	Random sequence generation	Allocation concealment	Blinding	Completeness of data
Eriksson and Granström[8]	+	−	−	+
Salminen et al.[13]	+	+	−	+
Styrud et al.[9]	+	+	−	−
Svensson et al.[14]	+	+	−	+
Vons et al.[12]	+	+	−	−

+, Low risk of bias; −, high risk of bias.

the other because of postrandomization exclusions that led to serious prognostic imbalance[11]. Four of the six authors (including the author of the quasi-RCT) confirmed the accuracy of the consensus data extraction, corrected some errors or provided additional information[10,12−14]; two[8,9] were unable to assist with the requests or could not be contacted.

Table 1 summarizes the characteristics of studies included in primary analyses. The five included RCTs had a total 1116 adult patients; four studies[8,9,12,13] recruited adults and one[14] children. The quasi-RCT[10] included 369 adults (*Tables S1* and *S2*, supporting information). Definitions of complications varied across the included studies, and were also different between the treatment groups in some studies (*Table S3*, supporting information). Postoperative

complications were reported consistently in all studies, but none used one of the common classification systems. For this review, complications were counted as minor or major based on their description in the original studies.

Histopathological diagnosis of acute appendicitis was made using standard criteria (mucosal inflammation) in one study[12], using stringent criteria in another (intra-mural inflammation required)[13], but remained unclear in most[8−10,14]. In the included trials, rates of negative appendicectomy varied from 0 to 15 per cent, with median of 3 per cent in the appendicectomy arms.

Risk-of-bias assessment

All studies probably generated random sequence adequately; one study likely failed to conceal randomization. None of the studies blinded patients, healthcare providers, outcome assessors or data analysts (*Table 2*; *Table S2*, supporting information). Loss to follow-up at 1 year was substantial, varying from 7 to 22 per cent, and was similar in the two groups within each study[8,12−14], although unclear in one study report[9].

Outcome assessment

Rate of appendicectomy within 1 month

Some 561 of the 562 patients allocated to surgery underwent appendicectomy (range across studies 99·6–100 per

Table 3 GRADE evidence profile: antibiotic therapy *versus* appendicectomy for acute non-perforated appendicitis

| No. of patients with data* Time frame | Quality assessment | | | | | Summary of findings | | | |
| | | | | | | Study event rates | | | |
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Antibiotic therapy	Appendicectomy	Absolute risk difference†	Certainty in estimates
Major complications									
999 (5) 1 year	Serious limitations: major and minor complications likely under-reported in antibiotics group	No serious limitations	No serious limitations	Serious limitations: 95% confidence interval crosses 0, indicating no difference	Undetected	25 of 510 (4·9)	41 of 489 (8·4)	−2·6 (−6·3, 1·1)% Favours antibiotic therapy	Low
Minor complications									
999 (5) 1 year	Serious limitations: major and minor complications likely under-reported in antibiotics group	Serious limitations: inconsistent forest plot estimates	No serious limitations	Serious limitations: 95% confidence interval crosses 0, indicating no difference	Undetected	11 of 510 (2·2)	61 of 489 (12·5)	−7·2 (−18·1, 3·8)% Favours antibiotic therapy	Very low
Recurrence of appendicitis									
999 (5) 1 year	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	114 of 510 (22·4)	0 of 489 (0)	22·6 (15·6 to 30·4)% Favours appendicectomy	High
Rate of appendicectomy within 1 month									
1112 (5) 1 month	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	47 of 550 (8·5)	561 of 562 (99·8)	91·8 (88·2, 94·8)% Favours antibiotic therapy	High
Length of hospital stay									
1100 (5) In hospital	No serious limitations	No serious limitations	Serious limitations: most patients operated on using open approach; laparoscopic approach would shorten length of hospital stay	No serious limitations	Undetected			0·41 (0·26 to 0·57) days Favours appendicectomy	Moderate
Length of sick leave									
1017 (3) 1 month	No serious limitations	Serious limitations: inconsistent forest plot estimates	Serious limitations: most patients operated on using open approach; laparoscopic approach would shorten length of sick leave	Serious limitations: 95% confidence interval crosses 0, indicating no difference	Undetected			−3·58 (−8·27, 1·11) days Favours antibiotic therapy	Very low

Values in parentheses are percentages unless indicated otherwise; values are *number of studies and †95 per cent confidence interval.

cent). The pooled estimate was 99·6 (95 per cent c.i. 98·9 to 100) per cent (high-quality evidence). Of the appendicectomies, 434 (77·4 per cent) were open and 127 (22·6 per cent) laparoscopic. Of the 550 patients allocated to antibiotic therapy, 47 underwent an appendicectomy within 1 month (range across studies 4·8–11·7 per cent). The pooled estimate was 8·2 (5·2 to 11·8) per cent (high-quality evidence) (*Table 3*).

Reference	Major complications		Weight (%)	Risk difference (%)	Risk difference (%)
	Antibiotics	Appendicectomy			
Eriksson and Granström[8]	1 of 20	1 of 20	7	0·0 (−13·5, 13·5)	
Salminen et al.[13]	6 of 227	11 of 215	44	−2·5 (−6·1, 1·1)	
Styrud et al.[9]	7 of 128	6 of 124	29	0·6 (−4·8, 6·1)	
Svensson et al.[14]	1 of 24	2 of 26	7	−3·5 (−16·5, 9·5)	
Vons et al.[12]	10 of 111	21 of 104	13	−11·2 (−20·6, −1·8)	
Total	25 of 510	41 of 489	100	−2·6 (−6·3, 1·1)	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.37$, 4 d.f., $P < 0.25$; $I^2 = 26\%$
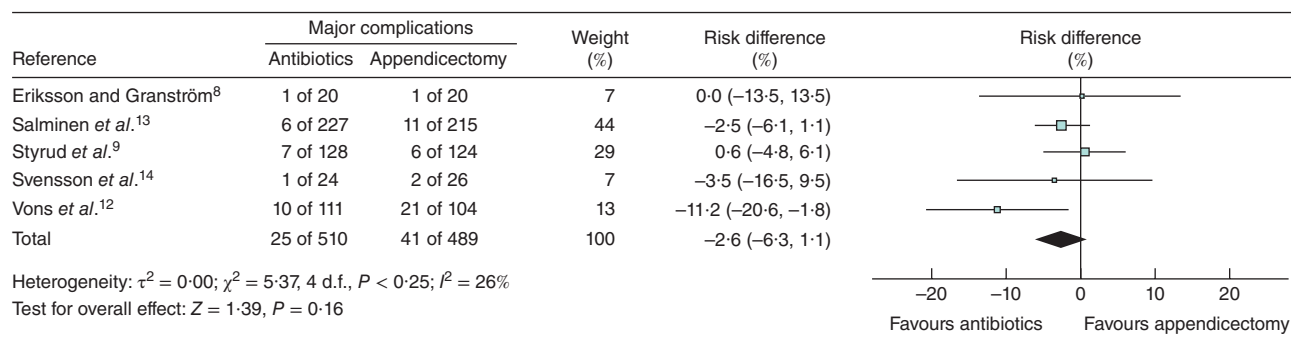Test for overall effect: $Z = 1.39$, $P = 0.16$

Fig. 2 Forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy group. Risk differences are shown with 95 per cent c.i.
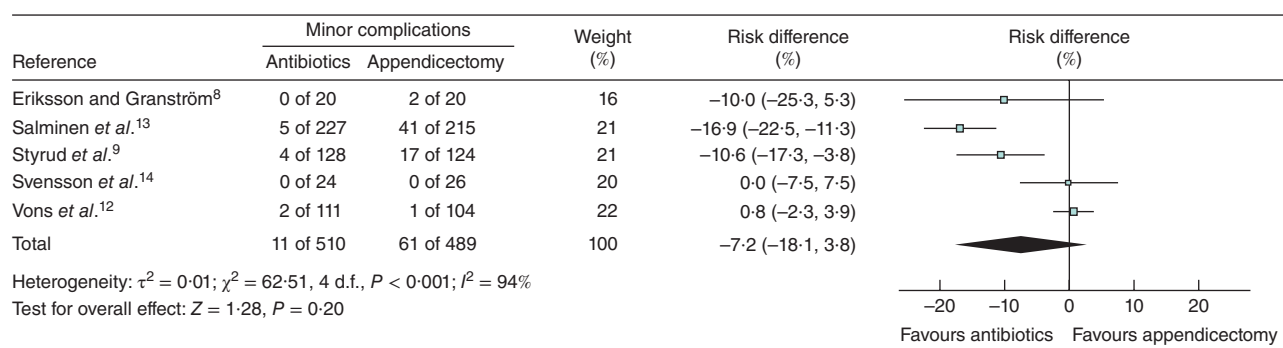
Reference	Minor complications		Weight (%)	Risk difference (%)	Risk difference (%)
	Antibiotics	Appendicectomy			
Eriksson and Granström[8]	0 of 20	2 of 20	16	−10·0 (−25·3, 5·3)	
Salminen et al.[13]	5 of 227	41 of 215	21	−16·9 (−22·5, −11·3)	
Styrud et al.[9]	4 of 128	17 of 124	21	−10·6 (−17·3, −3·8)	
Svensson et al.[14]	0 of 24	0 of 26	20	0·0 (−7·5, 7·5)	
Vons et al.[12]	2 of 111	1 of 104	22	0·8 (−2·3, 3·9)	
Total	11 of 510	61 of 489	100	−7·2 (−18·1, 3·8)	

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 62.51$, 4 d.f., $P < 0.001$; $I^2 = 94\%$
Test for overall effect: $Z = 1.28$, $P = 0.20$

Fig. 3 Forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy group. Risk differences are shown with 95 per cent c.i.

Major complications

Of the 510 patients allocated to antibiotic therapy, 25 had major complications *versus* 41 of 489 patients in the appendicectomy group: risk difference −2·6 (95 per cent c.i. −6·3 to 1·1) per cent (low-quality evidence) (*Fig. 2, Table 3*). Major complications in the appendicectomy group included 32 appendiceal perforations, five deep infections, two incisional hernias, one laparoscopic adhesiolysis and one death. Major complications in the antibiotic therapy group included 23 appendiceal perforations, one adhesive bowel obstruction and one death. The quality of evidence was rated as low because of imprecision and high risk of bias (*Table 3*).

Minor complications

Of the 510 patients allocated to antibiotic therapy, 11 had minor complications *versus* 61 of 489 patients in the appendicectomy group: risk difference −7·2 (95 per cent c.i. −18·1 to 3·8) per cent (very low-quality evidence) (*Fig. 3*). Minor complications included 38 superficial wound infections, 22 instances of abdominal or incisional discomfort at 1 year (reported only by Salminen and colleagues[13]), and

one case of diarrhoea in the appendicectomy group. Minor complications in the antibiotic group included three superficial wound infections, 4 instances of abdominal or incisional discomfort at 1 year (reported only by Salminen and colleagues[13]), and four complications that were not stated in more detail. None of the included trials reported any adverse effects of antibiotic treatment (such as diarrhoea or allergic reaction). The quality of evidence was rated as very low because of imprecision, inconsistency and high risk of bias in reporting complications (*Table 3*).

Recurrence of appendicitis within 1 year

None of the patients who underwent appendicectomy were reported to have recurrent appendicitis. The pooled estimate of recurrence in the antibiotic group, of whom 114 of 510 patients had a suspected or proven recurrence of appendicitis within 1 year, was 22·6 (15·6 to 30·4 per cent) (high-quality evidence) (*Table 3*). Of these 114 appendices, 14 (12·3 per cent) were not inflamed on subsequent histopathology. Average (mean or median) time from initial conservative treatment with antibiotics to recurrence varied between 3·4 and 7·0 months in the included trials.
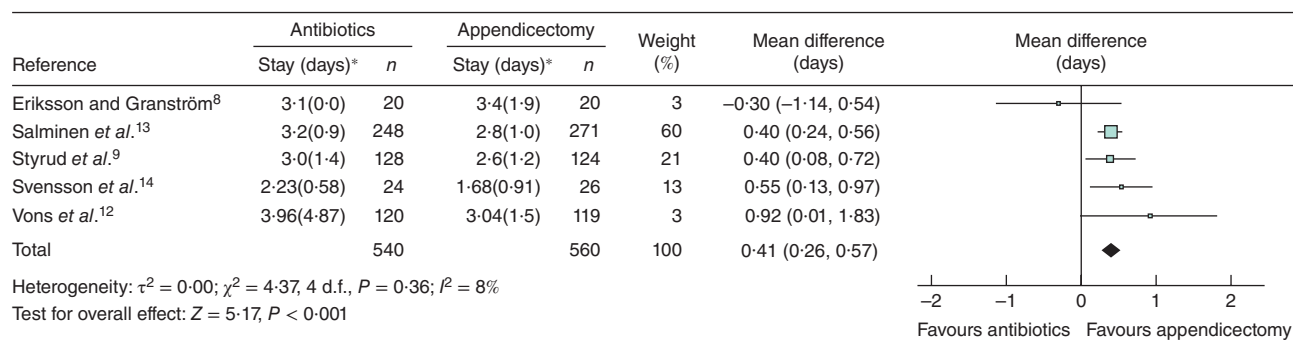
Reference	Antibiotics		Appendicectomy		Weight (%)	Mean difference (days)	Mean difference (days)
	Stay (days)*	n	Stay (days)*	n			
Eriksson and Granström[8]	3·1(0·0)	20	3·4(1·9)	20	3	−0·30 (−1·14, 0·54)	
Salminen et al.[13]	3·2(0·9)	248	2·8(1·0)	271	60	0·40 (0·24, 0·56)	
Styrud et al.[9]	3·0(1·4)	128	2·6(1·2)	124	21	0·40 (0·08, 0·72)	
Svensson et al.[14]	2·23(0·58)	24	1·68(0·91)	26	13	0·55 (0·13, 0·97)	
Vons et al.[12]	3·96(4·87)	120	3·04(1·5)	119	3	0·92 (0·01, 1·83)	
Total		540		560	100	0·41 (0·26, 0·57)	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.37$, 4 d.f., $P = 0.36$; $I^2 = 8\%$
Test for overall effect: $Z = 5.17$, $P < 0.001$

Fig. 4 Forest plot showing mean difference in length of hospital stay in antibiotic therapy *versus* appendicectomy group. Mean differences are shown with 95 per cent c.i. *Values are mean(s.d.)

Reference	Antibiotics		Appendicectomy		Weight (%)	Mean difference (days)	Mean difference (days)
	Leave (days)*	n	Leave (days)*	n			
Salminen et al.[13]	9·2(6·9)	256	17·0(8·3)	270	34	−7·80 (−9·10, −6·50)	
Styrud et al.[9]	8·0(8·0)	128	10·1(7·6)	124	33	−2·10 (−4·03, −0·17)	
Vons et al.[12]	9·82(10·51)	120	10·45(8·2)	119	32	−0·63 (−3·02, 1·76)	
Total		504		513	100	−3·58 (−8·27, 1·11)	

Heterogeneity: $\tau^2 = 16.22$; $\chi^2 = 39.29$, 2 d.f., $P < 0.001$; $I^2 = 95\%$
Test for overall effect: $Z = 1.50$, $P = 0.13$
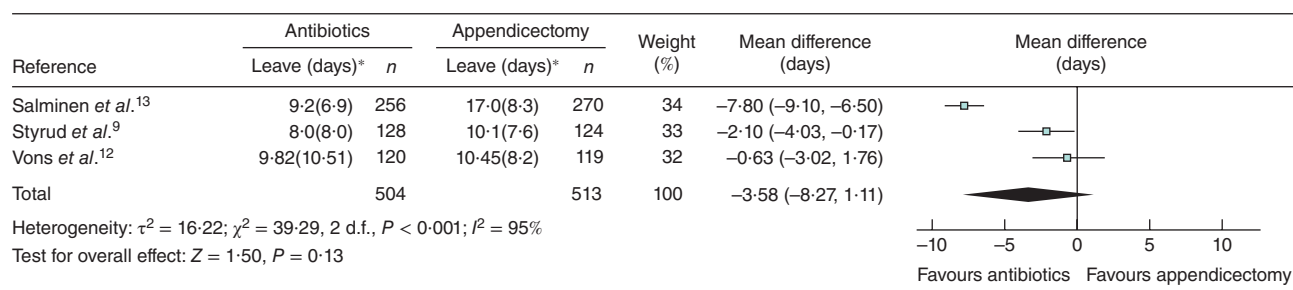
Fig. 5 Forest plot showing mean difference in length of sick leave in antibiotic therapy *versus* appendicectomy group. Mean differences are shown with 95 per cent c.i. *Values are mean(s.d.)

Duration of hospital stay

Three studies[8,9,12] reported, and two authors[13,14] later provided data on hospital stay. Patients in the appendicectomy arms had a modestly shorter duration of hospital stay: mean difference 0·41 (95 per cent c.i. 0·26 to 0·57) days (moderate-quality evidence) (*Fig. 4, Table 3*).

Duration of sick leave

Two studies[9,12] reported, and one author[13] later provided data on sick leave. One study[14] enrolled only children, and so sick leave was not applicable. The duration of sick leave did not differ materially between the groups; the mean difference was −3·58 (95 per cent c.i. −8·27 to 1·11) days, favouring antibiotic therapy (very low-quality evidence) (*Fig. 5, Table 3*).

Subgroup and sensitivity analyses

Neither the prespecified subgroup analyses nor the sensitivity analyses explained differences in minor or major complication rates (*Figs S1–S6*, supporting information).

Discussion

Five RCTs that followed more than 1100 patients with non-perforated appendicitis for 1 year demonstrated both advantages and disadvantages to an initial management strategy of antibiotics with appendicectomy only as necessary *versus* immediate appendicectomy. Advantages of the antibiotic regimen include a potentially lower rate of major complications (primarily appendiceal perforations) (2·6 per cent less, low-quality evidence), a potentially lower rate of minor complications (7·2 per cent less, very low-quality evidence), potentially shorter sick leave (4 days shorter, very low-quality evidence), and a lower rate of appendicectomies in the first month after presentation (91·8 per cent less, high-quality evidence). These advantages need to be traded off against a 22·6 per cent incidence of recurrence of appendicitis at 1 year (high-quality evidence) and potentially longer hospital stay (by 0·4 days, moderate-quality evidence) (*Table 3*).

Relative to previous systematic reviews, this analysis has many strengths. Use of explicit eligibility criteria led to the exclusion of two trials[11,33] inappropriately included in other reviews[16,22,23,25]: one that has been retracted owing to plagiarism[33] and another trial that suffered from serious prognostic imbalance[11]. A comprehensive search led to the inclusion of two recently published trials[13,14]. Two reviewers determined eligibility, assessed risk of bias, and abstracted data independently and in duplicate, with

adjudication by a third reviewer as necessary. Rigorous meta-analyses were conducted and prespecified subgroup effects were explored. Sensitivity analysis including a quasi-randomized study did not change the results appreciably. The GRADE approach[31,32] was applied to assess quality of evidence for each outcome (*Table 3*).

Limitations of this review are largely those of the primary studies. As the diagnosis of appendicitis was made without CT in three of the RCTs[8,9,14], they included patients with complicated appendicitis, and those without appendicitis at all. For studies that used CT, the rate of perforated appendix was variable: 18 per cent in the appendicectomy group in the French study[12], but only 1 per cent in the Finnish trial[13]. This could be due to inaccuracy of the CT scans or progression of initially non-perforated appendicitis. CT is far from perfect in differentiating complicated from uncomplicated appendicitis[34], whereas scoring systems might be more helpful in selecting patients in future trials[35].

The rate of operation in patients who did not have appendicitis on histopathology was very low in the included trials (0–3 per cent in most, and 15 per cent in 1 using clinical diagnosis only[8]). Although CT is limited in differentiating uncomplicated from complicated appendicitis, it has a high level of accuracy in differentiating patients with, and without appendicitis, leading to low rates of negative appendicectomy where CT was used routinely[36]. Another factor is that the threshold for the diagnosis of appendicitis based on histopathological findings (undefined in most of the studies) may have been low or very low. Only the Finnish study[13] reported use of stringent criteria, which require inflammation in the muscularis of the appendix. Such strict criteria have been reported to yield higher negative appendicectomy rates[37].

Risk of bias is a problem in all studies, with major limitations in some regarding allocation concealment, in all for blinding, and in many with respect to loss to follow-up. There were also reporting problems that required some inferences in data abstraction (for example no study classified complications according to their severity, thus requiring reviewers' inferences regarding whether complications were major or minor). All authors failed to report complications of antibiotic therapy (such as diarrhoea or allergic reactions) and most failed to report appendicectomy complications in detail in patients who initially received antibiotics, but who went on to have appendicectomy for recurrent appendicitis[8,9,12,13].

Enrolment was slow in two of the biggest trials[12,13], which recruited approximately one to three patients per month per hospital. The largest trial[13] was able to recruit less than 20 per cent of the patients treated for uncomplicated appendicitis in the trial hospitals during the enrolment period, and the study was actually terminated prematurely owing to slow enrolment. Thus, it is possible that only the least sick patients were enrolled in these trials. If that is so, the results of antibiotic treatment may not be as good if administered to sicker patients.

It is possible that some patients would prefer to avoid an appendicectomy because of rare but serious potential complications of general or spinal anaesthesia, but also because of possible short- and long-term pain associated with surgery, with decreased quality of life. Unfortunately, investigators did not measure pain consistently or rigorously, and did not report quality of life at all.

Generalizability to current clinical practice is also a concern. Only 22·6 per cent of procedures in the appendicectomy group were performed laparoscopically. Systematic reviews[38,39] of RCTs comparing open with laparoscopic appendicectomy have shown that the laparoscopic approach is associated with reduced wound infections, as well as a lower rate of bowel obstruction. As the majority of minor complications were wound infections and incisional discomfort, it is likely that a laparoscopic approach will reduce the rate of minor complications. Furthermore, more frequent use of a laparoscopic approach should shorten hospital stay and sick leave[38,39]. On the other hand, all RCTs reported in-hospital intravenous antibiotic treatment for 2–3 days, and it might be possible to reduce length of stay by using a different antibiotic regimen.

Other limitations included insufficient follow-up in all of the included studies. The rate of recurrent appendicitis was approximately 23 per cent during the first year; it is unknown how much this rate might rise with longer follow-up. Similarly, introducing broad-spectrum antibiotics to a large patient population carries the risk of worsening antibiotic resistance. It could be argued that antibiotics should be reserved for patients with a definitive diagnosis of uncomplicated appendicitis.

Despite the limitations of the available studies, they provide valuable evidence regarding the outcomes of antibiotic first *versus* immediate surgery for acute non-perforated appendicitis. The trade-off between the antibiotic-first approach – potentially 3 per cent fewer major complications, 7 per cent fewer minor complications, 4 days' shorter sick leave and 92 per cent fewer appendicectomies in the first month – must be balanced against the disadvantages: a 23 per cent recurrence rate within 1 year and slightly longer hospital stay (half a day). Patients averse to surgery are likely to choose an initial trial of antibiotics; those averse to the possibility of recurrence may prefer immediate appendicectomy. Ensuring that the decision is

consistent with patients' values and preferences requires shared decision-making[40].

Acknowledgements

References

1 Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990; **132**: 910–925.

2 Masoomi H, Nguyen NT, Dolich MO, Mills S, Carmichael JC, Stamos MJ. Laparoscopic appendectomy trends and outcomes in the United States: data from the Nationwide Inpatient Sample (NIS), 2004–2011. *Am Surg* 2014; **80**: 1074–1077.

3 Fitz RH. Perforating inflammation of the vermiform appendix: with special reference to its early diagnosis and treatment. *Am J Med Sci* 1886; **92**: 321–346.

4 McBurney C. Experience with early operative interference in cases of disease of the vermiform appendix. *NY Med J* 1889; **50**: 676–684.

5 Coldrey E. Treatment of acute appendicitis. *Br Med J* 1956; **2**: 1458–1461.

6 Combined traditional Chinese and western medicine in acute appendicitis. *Chin Med J (Engl)* 1977; **3**: 266–269.

7 Adams ML. The medical management of acute appendicitis in a nonsurgical environment: a retrospective case review. *Mil Med* 1990; **155**: 345–347.

8 Eriksson S, Granström L. Randomized controlled trial of appendicectomy *versus* antibiotic therapy for acute appendicitis. *Br J Surg* 1995; **82**: 166–169.

9 Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G *et al.* Appendectomy *versus* antibiotic treatment

in acute appendicitis. A prospective multicenter randomized controlled trial. *World J Surg* 2006; **30**: 1033–1037.

10 Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy *versus* appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009; **96**: 473–481.

11 Turhan AN, Kapan S, Kütükçü E, Yiğitbaş H, Hatipoğlu S, Aygün E. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009; **15**: 459–462.

12 Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B *et al.* Amoxicillin plus clavulanic acid *versus* appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011; **377**: 1573–1579.

13 Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T *et al.* Antibiotic therapy *vs* appendectomy for treatment of uncomplicated acute appendicitis. *JAMA* 2015; **313**: 2340–2349.

14 Svensson JF, Patkova B, Almström M, Naji H, Hall NJ, Eaton S *et al.* Nonoperative treatment with antibiotics *versus* surgery for acute nonperforated appendicitis in children. *Ann Surg* 2015; **261**: 67–71.

15 Kirby A, Hobson RP, Burke D, Cleveland V, Ford G, West RM. Appendicectomy for suspected uncomplicated appendicitis is associated with fewer complications than conservative antibiotic management: a meta-analysis of post-intervention complications. *J Infect* 2015; **70**: 105–110.

16 Liu ZH, Li C, Zhang XW, Kang L, Wang JP. Meta-analysis of the therapeutic effects of antibiotic *versus* appendicectomy for the treatment of acute appendicitis. *Exp Ther Med* 2014; **7**: 1–6.

17 Svensson J, Hall N, Eaton S, Pierro A, Wester T. A review of conservative treatment of acute appendicitis. *Eur J Pediatr Surg* 2012; **22**: 185–194.

18 Mason RJ, Moazzez A, Sohn H, Katkhouda N. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012; **13**: 74–84.

19 Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012; **344**: e2156.

20 Fitzmaurice G. Antibiotics *versus* appendectomy in the management of acute appendicitis: a review of the current evidence. *Can J Surg* 2011; **54**: 307–314.

21 Liu K, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery* 2011; **150**: 673–683.

22 Wilms IM, de Hoog DE, de Visser DC, Janzing HM. Appendectomy *versus* antibiotic treatment for acute appendicitis. *Cochrane Database Syst Rev* 2011; (11)CD008359.

23 Ansaloni L, Catena F, Coccolini F, Ercolani, Gazzotti F, Pasqualini E *et al*. Surgery *versus* conservative antibiotic treatment in acute appendicitis: a systematic review and meta-analysis of randomized controlled trials. *Dig Surg* 2011; **28**: 210–221.

24 Varadhan KK, Humes DJ, Neal KR, Lobo DN. Antibiotic therapy *versus* appendectomy for acute appendicitis: a meta-analysis. *World J Surg* 2010; **34**: 199–209.

25 Liu KL, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery* 2011; **150**: 673–683.

26 Karanicolas PJ, Montori VM, Devereaux PJ, Schünemann H, Guyatt GH. A new 'mechanistic–practical' framework for designing and interpreting randomized trials. *J Clin Epidemiol* 2009; **62**: 479–484.

27 Guyatt GH, Busse JW. *Modification of Cochrane Tool to Assess Risk of Bias in Randomized Trials*. http://distillercer.com/resources/ [accessed 6 September 2015].

28 Akl EA, Johnston BC, Alonso-Coello P, Neumann I, Ebrahim S, Briel M *et al*. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. *PLoS ONE* 2013; **8**: e57132.

29 Ebrahim S, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell *et al*. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. *J Clin Epidemiol* 2013; 66: 1014–1021.e1.

30 Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD *et al*. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. *J Clin Epidemiol* 2014; **67**: 560–570.

31 Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ *et al*. What is 'quality of evidence' and why is it important to clinicians? *BMJ* 2008; **336**: 995–998.

32 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924–926.

33 Malik AA, Bari SU. Conservative management of acute appendicitis. *J Gastrointest Surg* 2009; **13**: 966–970.

34 Leeuwenburgh MM, Wiezer MJ, Wiarda BM, Bouma WH, Phoa SS, Stockmann HB *et al*. Accuracy of MRI compared with ultrasound imaging and selective use of CT to discriminate simple from perforated appendicitis. *Br J Surg* 2014; **101**: e147–e155.

35 Atema JJ, van Rossem CC, Leeuwenburgh MM, Stoker J, Boermeester MA. Scoring system to distinguish uncomplicated from complicated acute appendicitis. *Br J Surg* 2015; **102**: 979–990.

36 Rao PM, Rhea JT, Rattner DW, Venus LG, Novelline RA. Introduction of appendiceal CT: impact on negative appendectomy and appendiceal perforation rates. *Ann Surg* 1999; **229**: 344–349.

37 Mariadason JG, Wang WN, Wallack MK, Belmonte A, Matari H. Negative appendicectomy rate as a quality metric in the management of appendicitis: impact of computed tomography, Alvarado score and the definition of negative appendicectomy. *Ann R Coll Surg Engl* 2012; **94**: 395–401.

38 Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic *versus* open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2010; (10)CD001546.

39 Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K. Meta-analysis of the results of randomized controlled trials that compared laparoscopic and open surgery for acute appendicitis. *J Gastrointest Surg* 2012; **16**: 1929–1939.

40 Flynn D, Knoedler MA, Hess EP, Murad MH, Erwin PJ, Montori VM *et al*. Engaging patients in health care decisions in the emergency department through shared decision-making: a systematic review. *Acad Emerg Med* 2012; **19**: 959–967.

Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search strategies (Word document)

Table S1 Characteristics of the study by Hansson and colleagues[10] (Word document)

Table S2 Risk of bias in the study by Hansson and colleagues[10] (Word document)

Table S3 Complications considered (Word document)

Fig. S1 Sensitivity analysis examining effect of inclusion of data from Hansson *et al.*[10]: forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy groups (Word document)

Fig. S2 Sensitivity analysis examining effect of inclusion of data from Hansson *et al.*[10]: forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy groups (Word document)

Fig. S3 Subgroup analysis of studies with or without CT confirmation of diagnosis: forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy groups (Word document)

Fig. S4 Subgroup analysis of studies with or without CT confirmation of diagnosis: forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy groups (Word document)

Fig. S5 Subgroup analysis according to completeness of data (high or low risk of bias): forest plot showing absolute risk difference in major complications in antibiotic therapy *versus* appendicectomy groups (Word document)

Fig. S6 Subgroup analysis according to completeness of data (high or low risk of bias): forest plot showing absolute risk difference in minor complications in antibiotic therapy *versus* appendicectomy groups (Word document)